

In the Specification:

Please amend the specification as follows:

At page 4, please replace the paragraph beginning at line 4 and extending to line 17 with the following replacement paragraph:

The invention provides a transgenic plant comprising a nucleic acid sequence of the invention, e.g., one having at least 95% sequence identity to SEQ ID NO:1. The transgenic plant can comprise a nucleic acid encoding a polypeptide capable of inhibiting apoptosis. The transgenic plant, as a result of expression of the nucleic acid of the invention, can become abiotic or biotic insult resistant. The biotic insult can be induced by a plant pathogen, such as a virus, a fungus, a bacteria or a ~~nemotode~~ nematode. The abiotic insult can be induced by high moisture, low moisture, salinity, nutrient deficiency, air pollution, high temperature, low temperature, soil toxicity, herbicides or insecticides. The transgenic plant, upon expressing a nucleic acid of the invention or being exposed to a polypeptide of the invention, can be phenotypically altered, e.g., wherein at least a portion of the plant exhibits a decreased level of senescence. The invention provides a seed capable of germinating into a plant having in its genome a heterologous nucleic acid sequence comprising a nucleic acid of the invention, e.g., one having at least 95% sequence identity to SEQ ID NO:1. The seed can comprise a nucleic acid encoding a polypeptide capable of inhibiting apoptosis in a plant cell.

At page 5, please replace the paragraph beginning at line 14 and extending to line 26 with the following replacement paragraph:

The invention provides a method for inhibiting apoptosis in a cell comprising the following steps: (a) providing an isolated or recombinant polypeptide having at least 95% sequence identity to SEQ ID NO:2, wherein the polypeptide is capable of inhibiting apoptosis in the cell, and, ~~[[a)]]~~ (b) contacting the polypeptide with the cell in an amount sufficient to inhibit apoptosis in the cell. The invention provides a method for inhibiting apoptosis in a cell comprising the following steps: (a) providing an isolated or recombinant nucleic acid comprising a sequence having at least 95% sequence identity to SEQ ID NO:1,

wherein the nucleic acid encodes polypeptide capable of inhibiting apoptosis in the cell, and, (b) contacting the nucleic acid with the cell and expressing the nucleic acid to produce an amount of polypeptide sufficient to inhibit apoptosis in the cell. In alternative aspects of these methods the cell can be an insect cell, e.g., a lepidopteran cell, such as a *Bombyx mori* cell or a *Spodoptera frugiperda* cell, and a coleopteran cell, a mammalian cell, or a plant cell.

At pages 5-6, please replace the paragraph beginning at line 27 of page 5 and extending to line 5 of page 6, with the following replacement paragraph:

The invention provides a method for identifying an agent that can modulate the activity of a polypeptide, wherein the polypeptide comprises a sequence having at least 95% sequence identity to SEQ ID NO:2 and is capable of inhibiting a caspase 9 protease, comprising: (a) providing an isolated or recombinant polypeptide comprising a sequence having at least 95% sequence identity to SEQ ID NO:2 that is capable of inhibiting a caspase 9 protease, and a test agent, (b) contacting the caspase 9 protease and polypeptide in the presence and absence of the test agent; and, (c), measuring the ability of the polypeptide to inhibit the caspase 9 protease in the presence and absence of the test agent, wherein an increase or decrease in the ability of the polypeptide to inhibit the caspase 9 protease in the presence of the test agent identifies the test agent as a modulator of the polypeptide's activity.

At page 6, please replace the paragraph beginning at line 6 and extending to line 21 with the following replacement paragraph:

The invention provides a method for identifying an agent that can modulate the activity of a polypeptide, wherein the polypeptide comprises a sequence having at least 95% sequence identity to SEQ ID NO:2 and is capable of inhibiting apoptosis in a cell, comprising: (a) contacting a cell expressing the polypeptide recombinantly in the presence and absence of a test agent before, during or after inducing apoptosis in the cell; and, (b) measuring the amount or degree of the polypeptide's activity in the cell in the presence and absence of the test agent, wherein an increase or decrease in the amount or degree of apoptosis in the test cell identifies the test agent as a modulator of the polypeptide's activity. In alternative aspects of these methods the cell can be an insect cell, e.g., a lepidopteran cell, such as a *Bombyx mori* cell or a *Spodoptera frugiperda* cell, or a coleopteran cell, a

mammalian cell, a yeast cell, a plant cell, and ther like. The degree of the polypeptide's activity in the cell can be determined by measuring the amount or degree of apoptosis in the cell; the amount or degree of caspase protease activity in the cell; the amount or degree of DNA fragmentation in the cell; the amount or degree of cleavage of substrates of caspases in the cell; or by measuring the amount or degree of any surrogate marker of apoptosis in the cell.

At pages 6-7, please replace the paragraph beginning at line 22 of page 6 and extending to line 6 of page 7 with the following replacement paragraph:

The invention provides a method of generating an abiotic or biotic insult-resistant plant comprising the following steps: (a) providing an isolated or recombinant polypeptide comprising a sequence having at least 95% sequence identity to SEQ ID NO:2, wherein the polypeptide is capable of inhibiting apoptosis in a plant cell, and, ~~[[a)]~~ (b) contacting the polypeptide with the plant in an amount sufficient to inhibit apoptosis in the plant, thereby generating a plant that is biotic insult resistant. The invention provides a method for generating an abiotic or biotic insult-resistant plant comprising the following steps: (a) providing an isolated or recombinant nucleic acid comprising a sequence having at least 95% sequence identity to SEQ ID NO:1, wherein the nucleic acid encodes a polypeptide capable of inhibiting apoptosis in a plant cell, and, (b) contacting the nucleic acid with the plant and expressing the nucleic acid to produce an amount of polypeptide sufficient to inhibit apoptosis in the plant. In alternative aspects of these methods, the biotic insult is induced by a plant pathogen, such as a virus, a fungus, a bacteria or a ~~nemotode~~ nematode. In alternative aspects of these methods, the abiotic insult is induced by high moisture, low moisture, salinity, nutrient deficiency, air pollution, high temperature, low temperature, soil toxicity, herbicides or insecticides.

At page 7, please replace the paragraph at lines 11-12 with the following replacement paragraph:

All publications, patents, patent applications, ~~[[GenBank]]~~ GenBank™ deposits, cited herein are expressly incorporated by reference for all purposes.

At pages 15-16, please replace the paragraph starting at line 30 of page 15 and extending to line 22 of page 16 with the following replacement paragraph:

The term percent “sequence identity,” in the context of two or more nucleic acids or polypeptide sequences refers to two or more sequences or subsequences that are the same or have a specified percentage of nucleotides (or amino acid residues) that are the same, when compared and aligned for maximum correspondence over a comparison window, as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. This definition also refers to the complement (antisense strand) of a sequence. For example, in alternative embodiments, nucleic acids within the scope of the invention include those with a nucleotide sequence identity that is at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% of the exemplary sequence set forth in SEQ ID NO:1. In alternative embodiments, polypeptides within the scope of the invention include those with an amino acid sequence identity that is at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% of the exemplary ~~sequences~~ sequence set forth in SEQ ID NO:2. Two sequences with these levels of identity are “substantially identical” and within the scope of the invention. Thus, if a nucleic acid sequence has the requisite sequence identity to SEQ ID NO:1, or a subsequence thereof, it also is a polynucleotide sequence within the scope of the invention. If a ~~polynucleotide~~ polypeptide sequence has the requisite sequence identity to SEQ ID NO:2, or a subsequence thereof, it also is a polypeptide within the scope of the invention. In one aspect, the percent identity exists over a region of the sequence that is at least about 25 nucleotides or amino acid residues in length, or, over a region that is at least about 50 to 100 nucleotides or amino acids in length. Parameters (including, *e.g.*, window sizes, gap penalties and the like) to be used in calculating “percent sequence identities” between two nucleic acids or polypeptides to identify and determine whether one is within the scope of the invention are described in detail, below.

At pages 20-21, please replace the paragraph at beginning at line 23 of page 20 and extending to line 7 of page 21 with the following replacement paragraph:

Expression vectors capable of expressing the nucleic acids and polypeptides of the invention in animal cells, including insect and mammalian cells, are well known in the art. Vectors which may be employed include recombinantly modified enveloped or non-enveloped DNA and RNA viruses, e.g., from ~~bauloviridae, parvoviridae, picornoviridae, herpesviridae, poxviridae, adenoviridae, picornaviridae~~ bauloviridae, parvoviridae, picornaviridae, herpesviridae, poxviridae, adenoviridae or alphaviridae. Insect cell expression systems commonly use recombinant variations of baculoviruses and other nucleopolyhedrovirus, e.g., *Bombyx mori* nucleopolyhedrovirus vectors (see, e.g., Choi (2000) Arch. Virol. 145:171-177). For example, Lepidopteran and Coleopteran cells are used to replicate baculoviruses to promote expression of foreign genes carried by baculoviruses, e.g., *Spodoptera frugiper*a cells are infected with recombinant *Autographa californica* nuclear polyhedrosis virus (AcNPV) carrying a heterologous, e.g., a human, coding sequence (see, e.g., Lee (2000) J. Virol. 74:11873-11880; Wu (2000) J. Biotechnol. 80:75-83). See, e.g., U.S. Patent No. 6,143,565, describing use of the polydnavirus of the parasitic wasp *Glyptapanteles indiensis* to stably integrate nucleic acid into the genome of Lepidopteran and Coleopteran insect cell lines. See also, U.S. Patne Nos. 6,130,074; 5,858,353; 5,004,687.

At page 28, please replace the paragraph beginning at line 21 and extending to line 29 with the following replacement paragraph:

*Protein expression and purification:* pGEX4T-1 plasmid was introduced into E. coli strain BL21 (DE3) containing the plasmid pT-Trx. Glutathione S-transferase (GST) fusion proteins were obtained by induction with 0.05 mM isopropyl  $\beta$ -thiogalactoside at 25°C for 8 hr and then purified using ~~glutathione-Sepharose~~ glutathione-Sepharose™ (see, e.g., Huang (2000) Proc. Natl. Acad. Sci. USA 97: 1427-1432). The catalytic domains of caspase-3, caspase-7 and caspase-9 were expressed, purified by Ni-chelation affinity-chromatography, and quantified as described by Stennicke (1997) J. Biol. Chem. 272: 25719-25723; Stennicke (1998) J. Biol. Chem 273: 27084-27090; Stennicke ~~(19999)~~ (1999) J. Biol. Chem. 274: 8359-8362.



At page 29, please delete the paragraph beginning at line 6 and extending to line 22 with the following replacement paragraph:

*Cell culture. Transfection and Apoptosis Assays:* Insect Sf-21 cells were maintained at 27°C in Excell 401 medium (JRH Biosciences, Lenexa, KS) supplemented with 2.5% FBS. vP35del, *Autographa californica* nuclear polyhedrosis virus (AcMNPV) containing a deletion in the apoptosis suppressor “p35” gene (35-kilodalton protein gene) (see, e.g., Lerch (1993) Nucleic Acids Res. 21:1753-1760) was propagated in TN-386 cells (see, e.g., Clem (1991) Science 254:1388-1390). Plasmids encoding full length or deletion mutants of BmIAP (1 ug) were co-transfected with 1 ug vP35del viral DNA into Sf-21 cells by using ~~Lipofectin~~ Lipofectin™ from GIBCO/BRL. Occlusion body formation was observed under light-microscopy 3 days post-transfection. HEK293 cells were maintained in DMEM (Irvine Scientific) supplemented with 10% FBS, 1 mM L-glutamine, and antibiotics. 293 cells ( $10^6$ ) were cotransfected by using Superfect™ (Qiagen) with 0.1 ug of green fluorescence protein (GFP) marker plasmid pEGFP (CLONTECH), 0.25 ug of either pcDNA3-Bax or pcDNA3-Fas and 1.5 ug of pcDNA3-myc-BmIAP. Both floating and adherent cells were recovered 24 to 36 hour post-transfection and pooled, and the percentage of GFP-positive cells with nuclear apoptotic morphology was determined by staining with 0.1 ug/ml 4'-6-diamidino-2-phenylindole (DAPI) (mean +/- S.D.; n = 3) as described by Takhashi (1998) J. Biol. Chem. 273-787-7790.

Please replace the paragraph at page 31 beginning at line 18 and extending to line 53 with the following replacement paragraph:

BmIAP coding region nucleotide sequence:

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1 ATGGAGTTGA CGAAAGTTGC TAAAAATGGA GCTGCCGCCA CGTTGGTGAT GTTAAAAAAT
61 GCGCGGGATG CAAAAATGCG ACCTTTCATT GGTCCGCTCA TGTTATCCTC GTGTGAGTCT
121 TCAACGACAT CCACACTCCC GTCACCTTCG TCGTCAGCTG ATAAAACGGA TAATCACGAC
181 ACATTCAACT TCCTTCCTGA TATGCCCCGAC ATGCGTCGTG AAGAGGAACG TCTGAAAACA
241 TTTGATCAGT GGCCCGTTAC GTTTTGTGACG CCGGAACAAT TGGCCCGCAA CGGATTCTAC
301 TACCTCGGTC GCGGCGACGA AGTGTGCTGT GCTTTCTGTA AGGTAGAAAT TATGAGGTGG
361 GTCGAAGGCG ACGATCCTGC CGCCGATCAT CGGAGATGGG CGCCCCAGTG TCCCTTTGTA
421 CGAAAACAAA TGTATGCCAA CGCTGGGGGA GAGGCGACCG CTGTCGGTAG AGACGAATGT
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481 GGGGCCAGTG CGGCCACGCA GCCTCCCCGC ATGCCCCGGCC CCGTGCACGC GCGGTACTCC  
541 ACCGAGGCCG CGCGGCTCGC CACCTTCAAG GACTGGCCGA GACGTATGCG CCAAAAACCC  
601 GAGGAACTGG CAGAGGCCGG ATTCTTCTAT ACAGGCCAAG GTGACAAAAC GAAATGCTTC  
661 TATTGCGACG GAGGGCTAAA AGATTGGGAA AGCGATGACG TTCCGTGGGA ACAGCACGCC  
721 AGATGGTTCG ACCGCTGCGC GTACGTGCAA TTGGTGAAAG GACGTGACTA CATTCAGAAG  
781 GTGAAGTCGG AGGCCACTGC GATATCTGCT AGCGAAGAAG AACAGGCCGC CACCAATGAT  
841 TCGACTAAGA ACGTCGCCCA AGAGGGCGAG AAACATTTGG ATGACTCTAA AATATGTAAA  
901 ATATGTTATT CCGAGGAGCG TAACGTGTGC TTCGTGCCGT GCGGCCACGT GGTGGCGTGC  
961 GCCAAGTGCG CGCTGTGCGAC GGACAAGTGC CCGATGTGTC GCAGGACGTT CACGAATGCG  
1021 GTGCGGCTCT ACTTCTCGTG A (SEQ ID NO:1)

Please replace the paragraph at page 32 beginning at line 19 and extending to line 33 with the following replacement paragraph:

The full-length BmIAP cDNA (SEQ ID NO:1) (~~Genbank~~ GenBank™ accession number AF281073) contains a continuous open reading frame (ORF) encoding a protein of 346 amino acids (Figure 1B). This ORF is initiated by an AUG within a favorable context for translation (see, e.g., Kozak (1996) Mammalian Genomes 7:563-574) and is preceded by upstream stop codons in all three reading frames. Figure 1A shows the location of the BIR domains (BIR1, residues 74 to 140, BIR2, residues 182 to 249; of SEQ ID NO:2) and the RING domain (residues 298 to 314; of SEQ ID NO:2) of BmIAP. Figure 1B is the full length amino acid sequence of BmIAP (SEQ ID NO:2). Sequence alignments of the BIR1 (Figure 1C), BIR2 (Figure 1D) and RING (Figure 1E) domains of BmIAP with the corresponding domains of other IAP family members are shown, with bold text ~~indicates~~ indicating identical amino acid. The ~~Genbank~~ GenBank™ accession numbers of sequences used for the alignments are *Bombyx mori* IAP (BmIAP) AF281073, *Spodoptera frugiperda* IAP (SfIAP) AF 186378, *Trichoplusia ni* IAP (TnIAP) AF195528, *Orgyia pseudotsugata* nucleopolyhedrovirus IAP (OpIAP) P41437, *Cydia pomonella* granulovirus IAP CpIAP) P41436, and *Drosophila melanogaster* IAP1 (DIAP1) Q24306.